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(54) Title: EFFERVESCENT DRUG DELIVERY SYSTEM FOR ORAL ADMINISTRATION

(57) Abstract

The pharmaceutical compositions of the present invention comprise orally administerable dosage forms that use effervescence as a penetration enhancer for drugs known, or suspected, of having poor bioavailability. Effervescence can occur in the stomach, once the tablet or other dosage form is ingested. In addition to effervescence in the stomach, or as alternative technique, by the use of appropriate coatings and other techniques, the effervescence can occur in other parts of the gastrointestinal tract, including, but not limited to, the esophagus, duodenum, and colon. The site of effervescence and drug release is chosen to correspond with the segment of the gastrointestinal tract displaying maximal absorption of the formulated drug, or to gain some other therapeutic advantage.

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EFFERVESCENT DRUG DELIVERY SYSTEM FOR ORAL ADMINISTRATION

BACKGROUND OF THE INVENTION

Many orally-administered drugs display poor bioavailability when administered in conventional dosage forms, *i.e.*, the rate and extent to which the drugs are absorbed is less than desirable. With several drugs, absorption may be as little as 30% or less of the orally administered dose. To compensate for this effect, a very large dose is often administered so that absorption of the therapeutically required quantity of the drug can occur. This technique may prove costly with expensive drugs; and the nonabsorbed drug may also have undesirable side effects within the gastrointestinal tract. In addition, poorly absorbed drugs often display large inter- and intrasubject variability in bioavailability. *See* Aungst, B.J., J. Pharm. Sci. 82:979-87, 1993. Specific examples (with the average bioavailability given in parentheses) include methyldopa (25%) with a range of 8% to 62%. *See* Kwan, K.C., Folz, E.L., Breault, G.O., Baer, J.E., Totaro, J.A., J. Pharmacol. Exp. Ther. 198:264-77, 1976; and nalbuphine (approximately 17%) with a range of 6% to 40%. *See* Lo. M.-W, Schary, W.L., Whitney, C.C., Jr., J. Clin. Pharmacol. 27:866-73, 1987. Such variation in the amount of drug absorbed does not allow for good control of the disease condition.

To improve the bioavailability of poorly absorbed drugs, penetration enhancers have also been employed. However, many of the penetration enhancers referred to in the current literature damage the absorbing tissues and thus are not a practical solution to the problem of poor bioavailability. In fact, it has been suggested that the damage to the mucosa caused by these agents may be the factor responsible for the improved absorption. *See* LeCluyse, E.L. and Sutton, S.C., Advanced Drug Delivery Reviews, 23:163-83, 1997.

Other techniques which have been employed to improve bioavailability include using enteric coated tablets having effervescence to rapidly dissolve or disperse the dosage form

in the stomach. *See* U.S. Patents Nos. 4,503,031; 4,289,751; and 3,961,041.

SUMMARY OF THE INVENTION

The pharmaceutical compositions of the present invention comprise orally administerable dosage forms that use effervescence as a penetration enhancer for drugs known, or suspected, of having poor bioavailability. Effervescence can occur in the stomach, once the tablet or other dosage form is ingested. In addition to effervescence in the stomach, or as alternative technique, by the use of appropriate coatings and other techniques, the effervescence can occur in other parts of the gastrointestinal tract, including, but not limited to, the esophagus, duodenum, intestinal and colon. The site of effervescence and drug release is chosen to correspond with the segment of the gastrointestinal tract displaying maximal absorption of the formulated drug, or to gain some other therapeutic advantage. Desirably, such site is not in the mouth of the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an enlarged top plan view of a tablet which has a bioconcaved shaped.

Fig. 2 is an enlarged side view of an enteric coated multilayered tablet.

Fig. 3 is an enlarged top view of an enteric coated multilayered tablet, which depicts the effervescent external to the mucous adhesive layer.

Fig. 4 is an enlarged top view of an enteric coated multilayered pellet, which depicts the effervescent external to the mucous adhesive layer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The pharmaceutical compositions of the present invention comprise orally administerable medicaments in combination with an effervescent as a penetration enhancer for influencing absorption of a drug in the gastrointestinal tract. Effervescence leads to an increase in the rate and/or the extent of absorption of the drugs that are known or suspected

of having poor bioavailability. It is believed that such increase can rise from one or all of the following mechanisms:

1. reducing the thickness and/or the viscosity of the mucus layer which is present adjacent to the gastrointestinal mucosa;
2. alteration of the tight junctions between cells, thus promoting absorption through the paracellular route;
3. inducing a change in the cell membrane structure, thus promoting transcellular absorption;
4. increasing the hydrophobic environment within the cellular membrane.

The present dosage forms include an amount of effervescent agent effective to aid in penetration of the drug in the gastrointestinal tract. The amount of effervescent employed must not merely permit rapid dispersion of the medicament in the gastrointestinal tract, but must aid in penetration of the drug across the gastrointestinal mucosa. The formulations of the present invention may be distinguished from other effervescent formulations that are enteric coated on the basis of the amount of effervescent material that they contain. Prior formulations contain approximately half to a quarter as much bicarbonate as drug on a weight basis (together with a proportionate amount of acid). In these cases, the small amount of effervescent couple serves only to rapidly disintegrate the tablet.

The dosage forms of the present invention should preferably contain at least twice as much sodium bicarbonate (or an equivalent amount of other base) as drug (on a weight basis) together with the proportionate amount of an appropriate acid for generating the effervescent reaction. More preferably the present dosage forms should contain at least three times as much sodium bicarbonate as drug (on a weight basis) together with the proportionate amount of an appropriate acid. These high concentrations of effervescent couple are needed to generate effervescence in sufficient amounts to promote permeability and absorption of the drug.

Preferably, the effervescent is provided in an amount of between about 5% and about 95% by weight, based on the weight of the finished tablet, and more preferably in an amount of between about 30% to about 60%. However, the amount of effervescent agent must be optimized for each specific drug.

The term "effervescent penetration enhancer" includes compounds which evolve gas. The preferred effervescent penetration enhancers evolve gas by means of a chemical reaction, which takes place upon exposure of the effervescent penetration enhancer to water and other fluids. Such water-activated materials must be kept in a generally anhydrous state and with little or no absorbed moisture or in a stable hydrated form, since exposure to water will prematurely disintegrate the tablet. The acid sources may be any which are safe for human consumption and may generally include food acids, acid and hydrite antacids such as, for example, citric, tartaric, amalic, fumeric, adipic, and succinics. Carbonate sources include dry solid carbonate and bicarbonate salt such as, preferably, sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like.

The effervescent penetration enhancers of the present invention are not limited to those which are based upon a reaction which forms carbon dioxide. Reactants which evolve oxygen or other gases and which are safe for human consumption are also considered within the scope of the present invention.

The present dosage forms may also include in amounts additional to that required for effervescence a pH adjusting substance. For drugs that are weakly acidic or weakly basic, the pH of the aqueous environment can influence the relative concentrations of the ionized and the unionized forms of the drug present in solution, according to the Henderson-Hasselbach equation. Th pH of solutions in which an effervescent couple with equimolar amounts of base and acid has dissolved is slightly acidic due to the evolution of CO_2. While it is impractical and may not be desirable to change the pH of the contents of the small intestine, it is, nevertheless, possible

to alter the pH of the local environment (intestinal contents in immediate contact with the tablet and any drug that may have dissolved from it). This is achieved by incorporating in the tablet certain pH adjusting substances. Thus, the relative proportions of the ionized and unionized forms of the drug may be controlled.

In this way the system can be optimized for each specific drug under consideration: if the drug is known, or suspected, to be absorbed through the cell membrane (transcellular absorption), it would be most appropriate to alter the pH of the local environment to a level that favors the unionized form of the drug. Conversely, if the ionized form is more readily dissolved, the local environment should favor ionization. Thus, for fentanyl, as a nonlimiting example, the pH is adjusted to neutral (or slightly higher) since the pKa is 7.3. At this pH, the aqueous solubility of this poorly water-soluble drug is not compromised unduly, yet allowing a sufficient concentration of the drug to be present in the unionized form. This facilitates the permeation enhancement brought about by effervescence. In the case of prochlorperazine (pKa=8.1), a slightly higher pH is required.

Suitable pH adjusting substance for use in the present invention include any weak acid or weak base (in amounts additional to that required for effervescence) or, preferably, any buffer system that is not harmful to the gastrointestinal mucosa. These include, but are not limited to, any of the acids or bases previously mentioned as the effervescent components, sodium carbonate, potassium carbonate, potassium carbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, and the equivalent potassium salts.

The active agents suitable for use in the present invention preferably includes any drug that displays poor bioavailability, slow absorption or long t_{max}. These active ingredients include small molecule drugs, nutritional supplements (such as vitamins and minerals), proteins and peptides and other substances of biological origin. Examples of such drugs include, but are not limited to, the following:

Drug	Bioavailability (%)
Acyclovir	15-30
Auranofin	15-25
Bretylium	23±9
Cyclosporine	23±7
Cytarabine	20
Doxepin	27±10
Doxorubicin	5
Hydralazine	16-35
Ketamine	20±7
Labetalol	18±5
Mercaptopurine	12±7
Methyldopa	25±16
Nalbuphine	25±16
Naloxone	2
Pentoxifylline	19±13
Pyridostigmine	14±3
Terbutaline	14±2
Verapamil	22±8
Riboflavin	11
Atenolol	50

Pharmaceutical ingredients suitable for use in the present dosage forms may include, without limitation, analgesics, anti-inflammatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antiasthmatics, antidiuretics, antiflatuents, antimigraine agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, beta blockers; peptides, proteins, oligonucleotides and other substances of biological origin, and combinations thereof. Also encompassed by the terms "active ingredient(s)", "pharmaceutical ingredient(s)" and "active agents" are the drugs and pharmaceutically active ingredients described in *Mantelle*, U.S. Patent No. 5,234,957, in columns 18 through 21. That text of *Mantelle* is hereby incorporated by reference. Alternatively or additionally, the

active ingredient can include drugs and other pharmaceutical ingredients, vitamins, minerals and dietary supplements as the same are defined in U.S. Patent No. 5,178,878, the disclosure of which is also incorporated by reference herein.

The dosage forms preferably contain materials that aid in releasing the drug in a specific section of the gastrointestinal tract, thus promoting site-specific delivery. There are various mechanisms by which such materials promote site-specific delivery and this invention is not limited to any one mechanism. For example, the material may be metabolized by enzymes present in a specific part of the gastrointestinal tract, thus releasing the drug in that section.

The materials used to promote site-specific absorption may preferably be included as coatings and/or as matrix materials. If a coating is used, it may be applied to the entire dosage form or to the individual particles of which it consists. Coating materials may be used to prevent the release of the active agent before the dosage form reaches the site of more efficient absorption.

The coating can also be used in conjunction with an effervescence to cause the effervescence to occur at specific areas of the gastrointestinal tract. Nonlimiting examples or coatings used in the present invention include: cellulose derivatives including cellulose acetate phthalate (CAP); shellac and certain materials sold under the trademark Eudragit™ (various grades may be used in specific combinations). Hydroxypropylmethyl cellulose phthallate in a grade that dissolves at pH 5 is the preferred coating material.

Precoating materials may also be used in the present invention. Nonlimiting examples include cellulose derivatives such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose or combinations and certain materials sold under the trademark Eudragit™ (various grades which may be combined). Hydroxypropylmethyl cellulose phthallate in a grade that dissolves at pH 5 is the preferred coating material.

Other materials may be used to aid in site specific delivery, and include, for example, sugars, polysaccharides, starches, polymers, etc. These compounds may be included as coatings or as matrix materials and aid in releasing the drug in specific sections of the gastrointestinal tract, thus promoting site-specific delivery.

Other ingredients or techniques may preferably be used with the present dosage forms to enhance the absorption of the pharmaceutical ingredient, to improve the disintegration profile, and/or to improve the organoleptic properties of the material and the like. These include, but are not limited to, the use of additional chemical penetration enhancers; absorption of the drug onto fine particles to promote absorption by specialized cells within the gastrointestinal tract (such as the M cells of Peyer's patches); ion pairing or complexation; and the use of lipid and/or surfactant drug carriers. The selected enhancement technique is preferably related to the route of drug absorption, *i.e.*, paracellular or transcellular.

A bioadhesive polymer may preferably be included in the drug delivery device to increase the contact time between the dosage form and the mucosa of the most efficiently absorbing section of the gastrointestinal tract. *See* Jonathan D. Eichman, "Mechanastic Studies on Effervescent-Induced Permeability Enhancement," University of Wisconsin-Madison (1997), hereby incorporated by reference. Nonlimiting examples of known bioadhesives used in the present invention include: carbopol (various grades), sodium carboxy methylcellulose, methylcellulose, polycarbophil (Noveon AA-1), hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium alginate, and sodium hyaluronate.

Disintegration agents may also be employed to aid in dispersion of the drug in the gastrointestinal tract. Disintegration agents include any pharmaceutically acceptable effervescent agent. In addition to the effervescence-producing disintegration agents, a dosage form according to the present

invention may include suitable noneffervescent disintegration agents. Nonlimiting examples of disintegration agents include: microcrystalline cellulose, croscarmelose sodium, crospovidone, starches and modified starches.

Apart from the effervescent material within the tablet, some additional effervescent components or, alternatively, only sodium bicarbonate (or other alkaline substance) may be present in the coating around the dosage form. The purpose of the latter effervescent/alkaline material is to react within the stomach contents and promote faster stomach emptying.

The drug delivery device may be in the form of a tablet, granules, pellets or other multiparticulates, capsules that can contain the drug in the form of minitablets, beads, or a powder, or any other suitable dosage form.

If tablets are used, they may be matrix tablets; layered tablets in which the various components are separated in different layers to optimize their benefits; or other specialized forms of tablets, including nonconventional shapes and geometric arrangements. One example of a nonconventional shape is a flat-faced tablet with a biconcave central zone, as depicted in Figure 1. The outer, thicker part of the tablet may contain the mucoadhesive material while the inner, thinner segment may contain the drug and effervescent components. This arrangement allows drug release to a segment of the gastrointestinal mucosa in close proximity to the point at which the tablet is attached to the mucosa.

The drug and/or the effervescent material could be present in a sustained release matrix. The whole tablet may consist of this matrix or the matrix may be confined to one, or more, layers of a multilayered tablet. Figure 2 depicts a multilayered tablet with a central layer containing the drug and optional effervescent material; and two mucoadhesive layers. The tablet would adhere to the mucosa irrespective of its spatial orientation within the intestine.

Figures 3 and 4 depict the effervescent layer external to the mucoadhesive layer of each dosage form. Figure 3 depicts a multilayered tablet in which a central core is completely

surrounded by each subsequent layer. Such a tablet may be prepared by a compression coating technique. A similar physical arrangement of layers can also be achieved in a spheroid or pellet which may be prepared by extrusion and spheronization, layering, coating or any combination of these techniques. (*See* Figure 4.) The effervescence will cause a thinning of the mucus layer from the gastrointestinal segment, thus facilitating adhesive of the dosage form to the cellular surface rather than to the mucus layer. This arrangement promotes better absorption of the drug.

Tablets can be manufactured by wet granulation, dry granulation, direct compression or any other tablet manufacturing technique. The tablet may be a layered tablet consisting of a layer of the active ingredients set forth above in layers of diverse compositions. In accordance with the present invention, the tablet size is preferably up to about ¾". In accordance with the present invention, the multiparticulate size is preferably up to about 3 mm. In accordance with the present invention, the tablet hardness is preferably between about 5 N and 100 N.

Excipient fillers can be used in connection with the present invention to facilitate tableting. Nonlimiting examples of fillers include: mannitol, dextrose, lactose, sucrose, and calcium carbonate.

Pellets or other multiparticulates may be manufactured by granulation, layering techniques, extrusion and spheronization or other pellet manufacturing methods. The multiparticulates are then coated with an enteric coating material as described for tablets. The coating is preferably done in a fluid bed coater. The preferred, but nonlimiting, coating material is hydroxypropylmethyl cellulose in a grade that dissolves at pH 5. The multiparticulates are then packed into capsules.

The granules may be made by a wet granulation process or a dry granulation process. When wet granulation is used, isopropyl alcohol, ethyl alcohol or other nonaqueous

granulating agent is used. Low moisture content grades of these organic solvents are used.

Dry granulation may be achieved through slugging or chilsonation. Layering may be done in a fluid bed apparatus or coating pan. Nonaqueous binders are used to aid the adherence of the added material (drug, effervescent penetration enhancer and excipients) to the starting material. Nonlimiting examples of the starting material or cores are nonpareils (sucrose) or microcrystalline cellulose seeds.

The preferred technique for the manufacture of multiparticulates is extrusion and spheronization. The beads contain the drug, effervescent couple (as previously described), a fine particle diluent which also aids in the formation of the beads (examples are lactose and mannitol) and a spheronization aid such as microcrystalline cellulose. The preferred grade of the latter is Avicel RC 591 which contains sodium carboxymethyl cellulose as an additional ingredient. For this formulation, a nonaqueous solvent is used. Nonlimiting examples of nonaqueous solvents are isopropanol and ethanol. Low moisture content grades are used.

The alternate (and preferred) formulation is to manufacture two populations of beads, one containing the acid component and the other the alkaline component of the effervescent couple. Each population of beads contains similar drug concentrations and can be manufactured using water. Care should be taken to ensure that each population of beads has a similar size range and a similar density. Equal densities may be achieved by the incorporation of a nontoxic material of high density to the population of beads that would, otherwise, have had a lower density. A nonlimiting example of such a material is barium sulfate. Equivalence of size and density facilitates the achievement of similar emptying rates of the beads from the stomach once the dosage forms are consumed by the subject. When the beads come into contact with the intestinal fluids, the coating dissolves and the close proximity of the beads to each other allows the effervescent reaction to occur *in situ*.

The coating applied to the dosage forms of the present invention must be performed with precision to avoid pinhole faults since water penetration through such faults leads to rapid and premature disintegration of the tablet. Such coating can be performed by one skilled in the art who, additionally, takes precautions to limit abrasion and chipping of the partially formed coat during the coating process. A fluid bed coater, pan coater or other coating apparatus may preferably be used.

The invention will be further described by reference to the following detailed examples. These examples are provided for the purposes of illustration only, and are not intended to be limiting unless otherwise specified.

EXAMPLE 1: RIBOFLAVIN

INGREDIENTS	mg/TABLET
Riboflavin, USP	5
Silicified Microcrystalline Cellulose	19.7
Sodium Bicarbonate	18.2
Citric Acid, Anhydrous	13
Crospovidone	3
Magnesium Stearate	0.9
Colloidal Silicon Dioxide	0.5
TOTAL	**60**

The tablets were compressed to a hardness of 50 N using 3/16-inch concave punches. The tablets had a friability of less than 0.25%. Coating solution was prepared according to the following formula:

INGREDIENTS	WEIGHT (gm)
Hydroxypropylmethyl cellulose phthallate	418.5
Triethylcitrate	31.5
Ethanol	2025.0
Acetone	2025.0
TOTAL	**4500.0**

Using a fluidized bed coater, the tablets were coated to a 15% weight gain. Care was taken to fluidize the bed sufficiently so that agglomeration of the tablets did not occur during coating but excessive movement was avoided to minimize chipping of the tablets or abrasion of the coating material.

EXAMPLE 2: ATENOLOL

INGREDIENTS	mg/PER TABLET
Atenolol	7.143
Sodium bicarbonate	15.000
Citric acid	10.714
Silicified microcrystalline cellulose	26.043
Magnesium stearate	0.900
Silicon dioxide	0.200
TOTAL	**60.000**

The tablets were compressed using 3/16-inch concave punches to a hardness of 40 N. The tablets were coated with hydroxypropylmethyl cellulose phthallate solution as described above to a weight gain of 15%. Seven tablets were packed into a size 0 elongated capsule to form the final dosage form.

EXAMPLE 3: ATENOLOL POPULATION 1

INGREDIENTS	mg PER CAPSULE
Atenolol	25
Sodium bicarbonate	150
Lactose	37
Avicel RC 591	38
Water	Qs
TOTAL	**250**

The dry powders were blended together. Water was slowly added with mixing until a wet mass that was plastic (but not tacky) was formed. The wet mass was passed through an extruder. The extruded material was spheronized for 3 minutes. The beads that were formed were air dried for one hour and then

dried in an oven at 35°C overnight. The beads were sieved to remove large particles and fines.

EXAMPLE 4: ATENOLOL POPULATION 2

INGREDIENTS	mg PER CAPSULE
Atenolol	25
Citric acid	107
Lactose	80
Avicel RC 591	38
Water	Qs
TOTAL	**250**

Population 2 was made in a similar fashion to population 1. Each population of beads was separately coated to a 20% weight gain in a fluidized bed coater using the previously described coating solution. Two hundred and fifty milligrams of each population of beads was filled into size 0 elongated capsules and this formed the final dosage form.

Various modifications of the invention described herein will become apparent to those skilled in the art. Such modifications are intended to fall within the scope of the appending claims.

INDUSTRIAL APPLICABILITY

The invention relates to the pharmaceutical and medical industries and to the production of dosage forms.

CLAIMS:

1. A dosage form for delivery of a therapeutically effective amount of a drug to a target area in the gastrointestinal tract of a mammal; comprising:

(a) a therapeutically effective amount of a drug;

(b) at least one effervescent penetration enhancer; wherein said at least one effervescent penetration enhancer is present in an amount sufficient to increases the penetration of said drug across said target area of said gastrointestinal tract to permit delivery of a therapeutically effective amount of said drug; and

(c) an enteric coating maintained over said drug and said at least one effervescent penetration enhancer; wherein said enteric coating prevents the release of said drug and said at least one effervescent penetration enhancer until a time at which said dosage form reaches said target area in said gastrointestinal tract.

2. The dosage form of claim 1, wherein said amount of said at least one effervescent penetration enhancer is equal to about two times the amount of said drug.

3. The dosage form of claim 1, wherein said amount of said at least one effervescent penetration enhancer is equal to about three times the amount of said drug.

4 The dosage form of any one of claims 1-3, further comprising a pH adjusting substance.

5. The dosage form of any one of claims 1-3, further comprising a bioadhesive, wherein said bioadhesive increases contact time between said drug and a mucosa layer of said target area.

6. The dosage form of clams 5, wherein said bioadhesive is contained in a portion of said dosage form external to said drug.

7. The dosage form of any one of claims 1-3, further comprising at least one noneffervescent penetration enhancer.

8. The dosage form of any one of claims 1-3 further comprising at least one disintegration agent, wherein said

disintegration agent causes the rapid dispersion of said drug to said target area of said gastrointestinal tract.

9. The dosage form of any one of claims 1-3, wherein said protective coating comprises a material that reacts with an enzyme present in said target area of the gastrointestinal tract to release said drug and said effervescent penetration enhancer.

10. The dosage form of any one of claims 1-3, wherein said dosage form is a tablet.

11. The dosage form of any one of claims 1-3, wherein said dosage form is a capsule.

12. The dosage form of any one of claims 1-3, wherein said dosage form is in the form of granules.

13. The dosage form of any one of claims 1-3, wherein said dosage from is in the form of pellets.

14. The dosage from of claim 10 wherein said tablet contains a biconcave zone central to two outer zones; wherein said drug and said effervescent penetration enhancer are located in said biconcave zone.

15. The dosage form of claim 14, wherein said two outer zones contain a bioadhesive.

16. The dosage form of claim 1, wherein said effervescent penetration enhancer comprises a pharmaceutically acceptable effervescent couple; said effervescent couple comprising an acid or equivalent thereof and a base or equivalent thereof.

17. The dosage form of claim 16 wherein said base is sodium bicarbonate.

18. The dosage form of claim 16 wherein said base or equivalent thereof is present in an amount equal to about two times the amount of said drug; and said acid is present in an amount approximately equimolar to said base.

19. The dosage form of claim 16 wherein said base or equivalent thereof is present in an amount equal to about three times the amount of said drug; and said acid is present in an amount approximately equimolar to said base.

20. The dosage form of claim 1 wherein said drug is a drug that displays poor bioavailability in said gastrointestinal tract.

21. A method for delivering a drug to a target area in the gastrointestinal tract of a mammal; comprising the steps of:

(a) orally administering a dosage form comprising a therapeutically effective amount of a drug and at least one effervescent penetration enhancer,

(b) causing said drug and said effervescent penetration enhancer to release from said dosage form at said target area in said gastrointestinal tract and to provide effervescent action at said target area; so that said effervescent action promotes the absorption of a therapeutically effective amount of said drug across said target area.

22. The method of claim 21 wherein said amount of said at least one effervescent penetration enhancer is about two times the amount of said drug.

23. The method of claim 22 wherein said amount of said at least one effervescent penetration enhancer is about three times the amount of said drug.

24. The method as claimed in claim 21 wherein said target area is selected from the group consisting of the stomach, duodenum, intestines, and the colon of the mammal.

25. The method of any one of claims 21-24, further comprising the step of administering a suitable pH adjusting substance in said dosage form.

FIG. 1

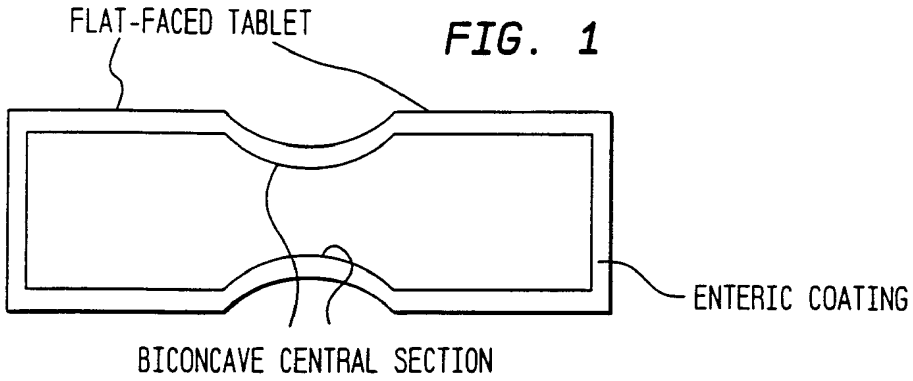


FIG. 2

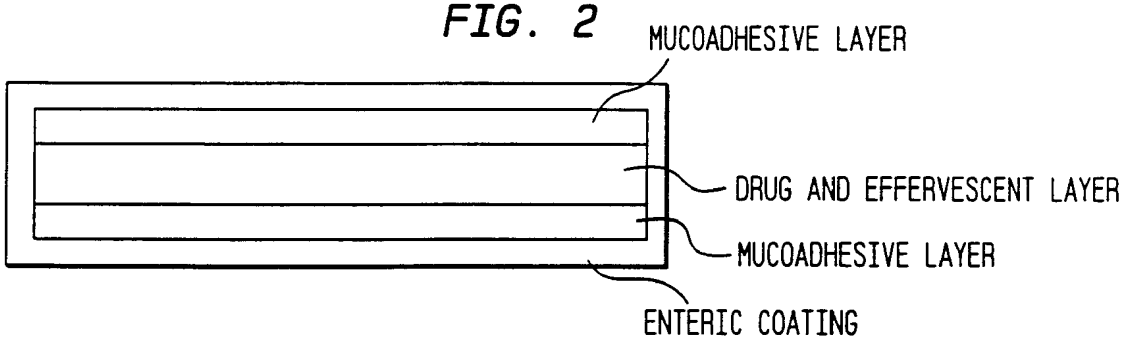


FIG. 3

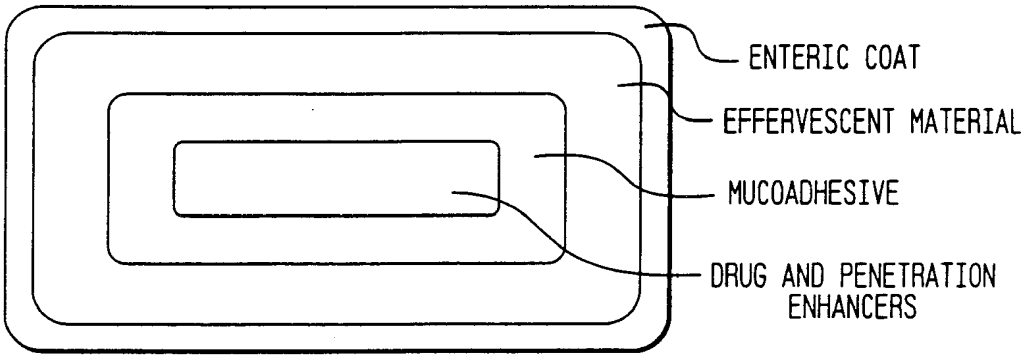
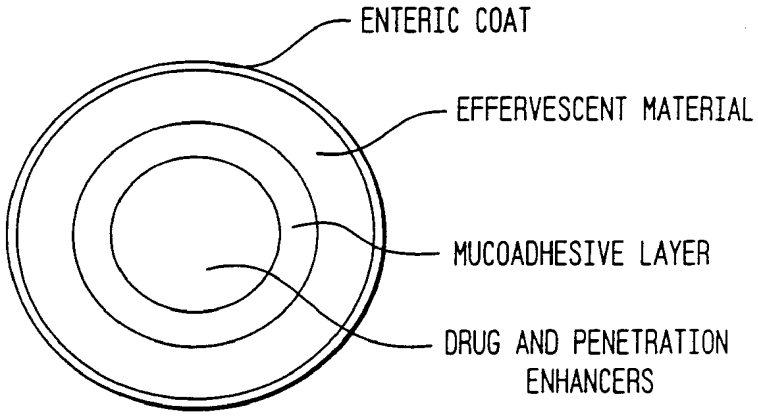


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/32, 9/36, 9/46
US CL :424/466, 480, 482

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/466, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,961,041 A (NISHIMURA et al) 01 June 1976, see entire document.	1, 8-10, 16, 17, 20, 21 and 24
X	US 4,289,751 A (WINDHEUSER) 15 September 1981, see entire document.	1, 8-10, 16, 17, 20, 21 and 24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 09 JUNE 2000	Date of mailing of the international search report 13 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-1235

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